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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/376,395	HUANG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,8*.
18)☐ Interview Summary (PTO-413) Paper No(s). _____.
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Applicant's election without traverse of group IV, claims 46-136, and of the species of asiaologlycoprotein, in Paper No. 10 is acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 113, 115, 116, 118-120, and 122-135 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33, 35-44, and 46. of U.S. Patent No. 6,008,202 ('202). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The invention claimed in '202' is a method of delivering to a cell in a human a drug/lipid/polycationic salt complex. See claims 1, 35, and 37. The complex may be formulated such that it has a positive charge excess of lipid and polycationic polypeptide to drug, and the drug may be a nucleic acid. See claims 2 and

8. Claims 113, 115, 116, 118-120, and 122-135 of the instant application are drawn to the same method and same compositions, except that they recite limitations concerning the route of administration of the complex, including intraperitoneal administration. Specific routes of administration are not claimed in '202'. However, '202' broadly claims methods of delivering the claimed complexes, and discloses a working example of intraperitoneal administration. For these reasons, intraperitoneal delivery of the instantly claimed compositions is obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 113, and 115-136 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims recite intratumoral, intratracheal, and intramuscular routes of administration. The specification provides no literal support for these routes of administration, so they represent new matter.

Enablement

Claims 46-136 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the E1A gene, at least one lipid species, and a polycationic polypeptide salt, wherein the composition has a net positive charge and for a method of administering the composition to an animal wherein the composition is delivered directly to the site of tumor cells intended to receive the E1A gene, does not reasonably provide enablement for a composition, or a method of administering the composition, wherein the composition comprises a net neutral or net negative charge, wherein the composition comprises any gene other than E1A, wherein the composition comprises a targeting ligand, or wherein the composition is administered systemically. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention encompasses compositions comprising a nucleic acid, at least one lipid species, and a polycationic polypeptide salt, and methods of making and using the compositions. Claims 46-76, 79, 83, and 117 require that the composition must have a net negative or neutral charge. Claims 77-112 require the use of a targeting ligand. Claims 113-136 encompass various routes of administration. All claims require the use of a nucleic acid as a drug. The specification defines the term "drug" at page 4, lines 15-18 as a molecular entity administered to an individual for the purpose of therapy. For this reason, the intended use of the claimed

compositions and methods is considered to be gene therapy. The specification does positively not assert any other utility for the claimed invention.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). Because the existing delivery and expression techniques cannot be used to predictably treat diseases, it is necessary for the specification to provide guidance to the skilled artisan as to how to overcome the factors which hamper gene delivery and expression such that a therapeutic result is achieved. It is noted

that because the claims encompass gene therapy generally, the scope which must be enabled is very broad and includes the treatment of any disease with any gene.

The specification teaches a working example of gene therapy in which the survival of mice injected intraperitoneally with tumor cells is prolonged by subsequent intraperitoneal administration of compositions comprising cationic polypeptides, lipids, and a nucleic acid encoding an E1A polypeptide. The specification fails to disclose the net charge of these compositions. See example 18, pages 53 and 54. US Patent 6,008,202, issued to Applicant, discloses the identical working example, and recites claims drawn to drug/lipid/polycationic polypeptide compositions comprising a net positive charge. See claim 2 of '202'. This patent is presumed to be valid, thus compositions comprising the net positive charge are presumed to be enabled. However, as one of skill in the art appreciates that most cells carry a net negative surface charge, delivery compositions of net negative or neutral charge would reasonably be expected to interact differently with target cells than would compositions of net positive charge. Clearly, the interaction of the composition with target cells is of critical importance to the function of the invention. In the absence of a targeting ligand, one of skill in the art would reasonably expect that the affinity of the net neutral or negative compositions for a given cell would be less than that of a positively charged composition. Because the specification does not disclose a working example of these compositions in gene therapy, and due to the unpredictability associated with the delivery of gene therapeutics as set forth by Orkin, Verma, and Anderson above, it is not clear that negative or neutral compositions would provide the same benefit as the positively

charged versions. Furthermore, the claims broadly encompass compositions and methods for the purpose of gene therapy in general. This scope encompasses the treatment of any disease, and with the exception of claims 56, 88 and 125 which recite the E1A gene, any gene may be used for treatment. However, the E1A gene is the only example of a therapeutic gene disclosed in the specification, and the specification teaches how to treat only one disease with this gene. In view of the broad scope encompassed by the claims, the unpredictability of the art of gene therapy, the uncertainty associated with the use of net negative or neutral particles, the disclosure of only a single therapeutic gene, and its use to treat only one disease, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Consideration of Example 18 also raises the issues of systemic versus local delivery, and the use of targeting ligands. This example employs direct injection at the site of the tumor, whereas the claims encompass systemic intravenous delivery. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al.(1995) reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain is a 1998 publication which

indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Crystal (1995) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus the general state of the art for targeted delivery of nucleic acids is immature in the context of therapeutic applications, necessitating direct administration of nucleic acids to the intended target site, rather than systemic administration.

The instant specification also contemplates receptor-mediated targeting of the claimed complexes. However, Perales et al (PNAS 91:4086-4090 (4/1994a)) teach that the unpredictability associated with receptor-mediated gene targeting is a major factor which prevents wider use of this approach in gene therapy protocols. These authors emphasize the need to "better characterize, the individual components of the DNA/ligand complex and to understand the nature of their assembly into a dependable vehicle for gene delivery." They also address the importance of the size of the ligand-bound delivery complex , noting that most endocytic

receptors discriminate against ligands of a determined size range *in vivo*. See page 4086, paragraph bridging columns 1 and 2, and column 2, first full paragraph. With specific respect to the asioaloglycoprotein receptor, the targeting ligand elected by Applicants, Schlepper-Schafer et al (Exp. Cell Res. (1986)) teach that ligands of greater than 7.8 nm in diameter are not taken up via this receptor. See abstract. In this context, it is noted that the instant specification fails to teach an example of the claimed compositions which is less than 35 nm in diameter, or to specifically contemplate a particle of the size which can be taken up by asialoglycoprotein receptor-mediated endocytosis. See Fig. 20. In fact, the specification teaches that the optimum size for coated pit internalization is 200 nm, thereby teaching away from a particle size which can be internalized by the asialoglycoprotein receptor. See page 11, lines 1 and 2.

Perales et al (Eur. J. Biochem. 226:255-266 (1994b) teach that, for receptor-mediated targeting to be useful in gene therapy, "it is critical that both the chemical properties and physical interactions of the reagents involved in the design of the DNA delivery vehicle be rigorously characterized." See abstract. In order to obtain particles of a size which can be internalized by asialoglycoprotein receptor-mediated endocytosis, it appears to be necessary to form particles comprising only a single DNA molecule complexed with the targeting ligand and polycation. See page 257, column 2, first and second full paragraphs. The formation of such complexes requires extremely low concentrations of DNA, the slow addition of a polycation comprising the targeting ligand, followed by titration with NaCl. Perales does not teach the use of lipids in combination with these complexes, as is required by the instant claims. The instant specification does not

contemplate the formation of the claimed complexes by addition of DNA to polycations in the absence of lipids as taught by Perales (1994a) (see e.g. page 17, lines 17-25), nor does the specification teach how to predict the effect of lipids on the particle size. On the contrary, Fig. 20 of the application shows that 50 different variations of the concentrations of the individual components of the complexes failed to produce particles of average size of less than 150 nm, and there is no clear trend which would allow one of skill in the art to predict how such a complex might be formed using the methods of the instant invention. Reduction of the lipid:DNA ratio resulted in a decrease in particle size to 35 nm, (see Table 4 on page 38), but again, the lack of any trend in these results would not allow one of skill in the art to predict how to form a complex of the appropriate size taught by Schlepper-Schafer. The specification also fails to address the possible effects of adding shielding components such as polyethylene glycol to the complex as required by claims 95 and 97.

In Genentech Inc. v Novo Nordisk A/S, the court found that when the specification omits any of the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See , e.g. , Hybritech Inc. v. Monoclonal Antibodies, Inc. , 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the size limitations on the ligand complex which are required for use of the use of asialoglycoprotein as a targeting ligand are critical to the practice of the invention and cannot be considered minor details which can be omitted in the process of providing an enabling disclosure.

In summary, the specification fails to disclose a working example of delivery compositions comprising a net negative or neutral charge, a working example of any composition comprising a targeting ligand, adequate guidance as to how to make and use a composition in which asioaloglycoprotein functions as a targeting ligand, or adequate guidance as to how to use the claimed compositions and methods for therapy by systemic administration. In view of the unpredictability of gene therapy, particularly with regard to the use of neutral or negatively charged nucleic acid complexes and targeted complexes, and the teachings in the art which show that the targeted compositions as envisioned by the specification are likely to be non-functional, one of skill in the art could not practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49, 52-54, 57-59, 68, 70, 71, 73, 76, 80-86, 89, 90, 91, 100, 101, 103, 106, 110-112, 118-123, and 126-128 are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49, 52-54, 59, 68, 73, 76, 81-86, 91, 103, 106, 110-112, 118-123, and 128 are indefinite because they recite "the polycationic polypeptide" without antecedent basis. The independent claims from which these claims depend recite "at least one polycationic polypeptide", therefore one of skill in the art cannot know which one of the "at least one" polycationic polypeptides is referred to in the claims.

Claims 57, 58, 68, 70, 71,76 ,89, 90, 100, 101, 106, 126, and 127 are indefinite because they recite "the lipid" without antecedent basis. The independent claims from which these claims depend recite "at least one lipid", therefore one of skill in the art cannot know which one of the "at least one" lipid is referred to in the claims.

Claims 49, 80, and 118 are indefinite because they recite the phrase "at least about". The words "at least" require a lower limit on the amount of an article in a composition. However, the word "about" renders the lower limit indefinite. One of skill in the art cannot know what is the lower limit of the intended range. Deletion of the word "about" is recommended.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

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